MARTINDALE

The Extra Pharmacopoeia

Thirty-first Edition

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Introduction continued

rary and repeated administration may be impractical. Local infiltration of anaesthetic at the site of operation is a simple method of preventing postoperative wound pain. Central nerve blocks obtained with epidural or intrathecal) administration of local anaesthetics produces excellent analgesia and use of a long-acting agent such as bupivacaine can produce prolonged pain relief. Insertion of a catheter during the operation allows subsequent administration by infusion or bolus injection. Hypotension is a potentially serious problem with central nerve blocks which necessitates constant monitoring of blood pressure. Administration of mixtures of opioids and local anaesthetics epidurally or intrathecally has permitted good postoperative analgesia to be obtained in some situations using relatively smaller doses of each agent. A wide range of other drugs such as clonidine have also been tried by these routes either alone or with opioids or local anaesthetics, but their role, if any, remains to be determined.

There is evidence that pre-operative administration (pre-emptive analgesia) of NSAIDs, opioids, local anaesthetic nerve blocks, epidural local anaesthetics, or various combinations of these may reduce postoperative pain; opioid premedication combined with a perioperative nerve block has also been effective. However, more studies are needed.

For some references to the management of postoperative pain, see below.

For further information on the agents mentioned above, see
Bupivacaine, p.1324
Buprenorphine, p.26
Butorphanol, p.27
Clonidine, p.843
Diamorphine, p.34
Diclofenac, p.36
Fentanyl, p.43
Ketorolac, p.56
Local Anaesthetics, p.1317
Nefopam, p.59
Pentazocine, p.85
Pethidine, p.86
Piroxicam, p.91
Meptazinol, p.59
Morphine, p.63
NSAIDs, p.72
Nalbuphine, p.68
Opioid Analgesics, p.75

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Sickle-cell crisis. The management of pain of sickle-cell crisis is similar to that of other forms of acute pain. The pain of mild crises may be controlled using analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or weak opioid analgesics. Crises severe enough to necessitate hospital admission usually require the use of stronger opioid analgesics but use with NSAIDs may potentiate analgesia and allow lower doses of opioids to be used.[1] Inhalation of a mixture of nitrous oxide 50% v/v and oxygen 50% v/v may be a useful analgesic during transfer to hospital.[2] Partial agonist and antagonist opioids such as buprenorphine or pentazocine are not recommended to treat acute pain before transfer to hospital.[3] Some patients appear to prefer pethidine to morphine[4] but control of pain may be inadequate and doses commonly used to manage crises may lead to accumulation of its neuroexcitatory metabolite and precipitate seizures[4,5] (see also p.86). As the dose of opioid required to control the pain can vary considerably, not only during each episode but also from one episode to another and between individual patients, some workers[6] have found patient-controlled analgesia (PCA) to be of help to manage the pain once initial pain relief has been obtained with loading doses of parenteral opioids. The use of continuous epidural analgesia with local anaesthetics alone or in combination with opioids is being studied.[7]

A recent double-blind study appeared to indicate that high doses of methyl prednisolone might shorten the duration of painful crises but there was a suggestion that there might be a rebound phenomenon with treated patients more likely to experience further crises soon after discharge.[8]

For a discussion of the overall treatment of sickle-cell crisis see under Haemoglobinopathies, p.746.

For further information on the agents mentioned above, see
Buprenorphine, p.26
Local Anaesthetics, p.1317
Methylprednisolone, p.1052
Morphine, p.63
NSAIDs, p.72
Nitrous Oxide, p.1260
Opioid Analgesics, p.75
Pentazocine, p.85
Pethidine, p.86

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8. Griffin TC, *et al.* High-dose intravenous methylprednisolone therapy for pain in children and adolescents with sickle cell disease. *N Engl J Med* 1994; 330: 733–7.

Sympathetic pain syndromes. Reflex sympathetic dystrophy (also referred to as complex regional pain syndrome type 1, algodystrophy, Sudeck's atrophy, post-traumatic osteoporosis, or shoulder-hand syndrome) is a severely painful syndrome of the limbs. Patients with reflex sympathetic dystrophy who respond to a sympatholytic procedure (see below) have been described as having 'sympathetically maintained pain' while those who do not as having 'sympathetic-independent pain'. Reflex sympathetic dystrophy is usually precipitated by injury or follows lack of use of the affected limb. There may be accompanying autonomic hyperactivity and trophic changes of skin and bone. Causalgia may be regarded as a specific type of reflex sympathetic dystrophy which follows damage to a peripheral nerve. The pain is continuous, diffuse, and burning, and is easily exacerbated. Its onset can be within days or weeks of an initial injury.

Management of reflex sympathetic dystrophy involves trying to restore normal function by treating the causative injury and easing the acute pain, followed by sympathetic nerve block with a local anaesthetic and aggressive physiotherapy as it is important that the patient starts using the affected limb again. Neurolytic nerve block with phenol has been tried and intravenous regional sympathetic block with the adrenergic blocking agent guanethidine may be useful. Stimulation techniques such as transcutaneous electrical nerve stimulation have been employed in some patients. Alpha blockers such as phenoxybenzamine or high doses of corticosteroids might produce some improvement. In refractory patients it might be worth trying antidepressants, antiepileptics, and other agents used in the general treatment of neurogenic pain (see under Postherpetic Neuralgia, above).

For some references to the management of sympathetic pain syndromes, see below.

For further information on the agents mentioned above, see
Antidepressants, p.299
Antiepileptics, p.363
Corticosteroids, p.1017
Guanethidine, p.877
Local Anaesthetics, p.1317
Phenol, p.1140
Phenoxybenzamine, p.928

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4. Scholl GD. An unsympathetic view of pain. *Lancet* 1995; 345: 630–6.
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6. Paice E. Reflex sympathetic dystrophy. *Br Med J* 1995; 310: 1645–8.

Trigeminal neuralgia. Trigeminal neuralgia (also known as tic douloureux) is a sudden, brief, sharp, agonising, episodic pain in the distribution of one or more branches of the fifth cranial nerve. There may be several episodes (lasting several seconds or minutes) a day over a number of weeks, followed by a pain-free interval which may last for weeks or years. Trigeminal neuralgia generally has a 'trigger zone' in which even a very light stimulus such as a draught of air produces pain. In some cases firm pressure applied around but not to the zone itself may help to relieve pain. Trigeminal neuralgia may be idiopathic or may be secondary to nerve compression (such as that caused by a tumour), facial injury, or multiple sclerosis.

The management of trigeminal neuralgia has been discussed in a number of reviews.[1-4] Carbamazepine is the drug of first choice and initially may produce satisfactory pain relief in 70% or more of patients. However, increasingly larger doses may be required. Also side-effects can be troublesome. If pain relief is inadequate then the addition of phenytoin may help; baclofen has also been added to carbamazepine therapy.[5] These agents may also be used alone or together in patients intolerant of carbamazepine. Other antiepileptics such as sodium valproate and clonazepam have also been used in carbamazepine-intolerant patients; oxcarbazepine is another possible alternative. Other agents that have been tried with some success in trigeminal neuralgia resistant to standard therapy include pimozide.[6]

In many patients drug therapy eventually fails to control the pain or produces unacceptable side-effects and invasive procedures become necessary. One method frequently used is the selective destruction of pain bearing nerve fibres with radiofrequency thermocoagulation; instillation of glycerol has also been used to achieve the same effect but the efficacy and safety of the procedure is debatable.[1,2]

For further information on the agents mentioned above, see
Baclofen, p.1515
Carbamazepine, p.368
Clonazepam, p.372
Glycerol, p.1711
Oxcarbazepine, p.376
Phenytoin, p.380
Pimozide, p.728
Sodium Valproate, p.388

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Musculoskeletal and Joint Disorders

The rheumatic diseases are a wide range of painful disorders affecting primarily the joints and related structures of the musculoskeletal system but there may also be widespread involvement of other systems. The term arthritis is used when the disease is largely confined to the joints. Some of the most common forms of arthritis are discussed below and these include rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, and the spondyloarthropathies such as ankylosing spondylitis. Other conditions which are associated with arthritis and which are discussed elsewhere include gout (p.419) and systemic lupus erythematosus (p.1026).

The names soft-tissue rheumatism and non-articular rheumatism, have been used to describe a number of painful conditions associated with disease of the structures that surround a joint. Such conditions considered in this category include fibromyalgia (fibrositis, muscular rheumatism, myofascial pain), humeral epicondylitis (e.g. tennis or golfer's elbow), frozen shoulder, Tietze's syndrome, fasciitis, tendinitis, tenosynovitis, bursitis (e.g. housemaid's knee), and sprains and strains.

Soft-tissue rheumatism has a variety of causes and may be associated with overuse, trauma, infection, or systemic inflammatory diseases. Inflammed or displaced tissue may impinge on nearby nerves and produce compression neuropathies such as carpal tunnel syndrome. Soft-tissue rheumatic conditions are usually benign and can remit spontaneously. The management of some of

these conditions has been reviewed.[1-3] Most will respond to selective rest of the affected region and splinting where appropriate. Gentle exercise, massage, application of heat, cold, or rubefacients can also be of benefit. Many soft tissue lesions respond to local injection of a corticosteroid given with a local anaesthetic. Some[4] have advocated the use of pyridoxine for patients with carpal tunnel syndrome: although some symptoms were reduced by pyridoxine in a recent study no difference in outcome was detected when compared with placebo.[5] There have been anecdotal reports of beneficial responses of carpal tunnel syndrome to hormone replacement therapy.[6,7] Short-term use of nonsteroidal anti-inflammatory drugs may help to relieve pain and reduce inflammation of soft tissue trauma. However, some conditions such as fibromyalgia, which is a chronic or recurrent condition characterised by diffuse musculoskeletal pain and the presence of tender trigger spots in periarticular muscles, respond poorly to analgesics and anti-inflammatory drugs. Patients with fibromyalgia also have disturbed sleep. Pain and sleep quality may be improved by tricyclic antidepressants such as amitriptyline or muscle relaxants such as cyclobenzaprine.[10] It has been recommended[11] that if these agents are ineffective after a trial of 4 to 6 weeks further drug treatment should be avoided. Fluoxetine has been tried as an alternative to tricyclic antidepressants.

Low back pain (sometimes referred to by the lay term lumbago), is an extremely common complaint in the industrialised world but only a small percentage of patients suffer from a recognised organic disease. The most frequent identifiable causes include mechanical or degenerative damage (e.g. disc disease), inflammatory diseases, infections, neoplasms, and bone diseases (e.g. osteoporosis, osteomalacia, Paget's disease). Of these, disc disease appears to be the most common major disorder seen in back pain clinics. In patients with a herniated or prolapsed disc the rupture of one of the fibrocartilageous intervertebral discs can exert pressure on spinal nerves and produce a condition characterised by severe and often acute pain radiating from the back along the distribution of the nerves affected. In lumbar disc herniation the sciatic nerve may be involved and patients experience pain (sciatica) usually in one leg along the typical distribution of the nerve. The evaluation and treatment of low back pain has been reviewed.[12-15] Where possible the underlying condition should be treated but the general treatment of acute back pain usually includes bed rest for a couple of days, physiotherapy, and analgesics to control the pain. However, there is evidence[16] to suggest that for patients with acute low back pain, continuing ordinary activities within the limits permitted by the pain, may lead to more rapid recovery than either bed rest or exercise. Muscle relaxants, such as diazepam, may also be of benefit but should only be given for a few days. Local injections of corticosteroids with local anaesthetics have been used but may have little to offer. Some advocate the use of epidural injections of corticosteroids but they have more often been used for chronic back pain and their use is considered to be controversial. Exercise and manipulation can be beneficial in chronic back pain; tricyclic antidepressants may sometimes be of help. Transcutaneous nerve stimulation, acupuncture, and neurolytic nerve blocks are other methods that have been tried for intractable chronic back pain. Surgery is indicated in patients with herniated disc if the general measures for treatment of low back pain fail or if there is severe nerve compression. Dissolution of the disc by injection of enzymes (chemonucleosis) such as chymopapain or collagenase appears to be an effective alternative to surgery, but anaphylactic reactions may occasionally occur.

For further information on the agents mentioned above, see

Amitriptyline, p.301	Fluoxetine, p.312
Chymopapain, p.1689	Local Anaesthetics, p.1317
Collagenase, p.1693	NSAIDs p.72
Corticosteroids, p.1017	Pyridoxine, p.1384
Cyclobenzaprine, p.1519	Tricyclic Antidepressants
Diazepam, p.700	(Amitriptyline, p.301)

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Ectopic ossification. For the use of nonsteroidal anti-inflammatory drugs in the prevention of ectopic ossification, see p.773.

Gout. For the treatment of gout, see p.419.

Juvenile chronic arthritis. Juvenile chronic arthritis is a general term used to describe a group of diseases characterised by joint inflammation of at least 3 months duration which occur in children under 16 years of age. The name Still's disease has been used rather inconsistently to describe some types of juvenile chronic arthritis.

Methods of treatment are generally the same as for rheumatoid arthritis in adults (see below), although for some therapeutic agents there is limited experience of their use in children. Some references to the management of juvenile chronic arthritis are given below.

1. Rosenberg AM. Advanced drug therapy for juvenile rheumatoid arthritis. *J Pediatr* 1989; 114: 173–8.
2. Rose CD, Doughty RA. Pharmacological management of juvenile rheumatoid arthritis. *Drugs* 1992; 43: 649–62.
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4. Kalla AA, *et al.* A risk-benefit assessment of slow-acting antirheumatic drugs in rheumatoid arthritis. *Drug Safety* 1994; 11: 21–36.
5. Southwood TR. Arthritis in children. *Br Med J* 1995; 310: 728–32.

Osteoarthritis. Osteoarthritis is a diverse collection of diseases also known as osteoarthrosis, degenerative joint disease, or joint failure. It is characterised by progressive disintegration of articular cartilage, usually accompanied by new bone formation at joint margins and beneath the involved cartilage. There may be synovial inflammation, particularly in advanced disease, but it is different in nature to that seen with rheumatoid arthritis and is usually only a minor component of the disease. Osteoarthritis may be a sequel to trauma, inflammation, or metabolic disorders, but usually the underlying origin is not apparent.

The options for the management of osteoarthritis have been reviewed.[1-3] It has been noted that although there have been claims based largely on *animal* studies that various agents are chondroprotective there is no evidence from controlled studies in humans that any treatment is disease-modifying.[4,5] Management is therefore aimed at relief of pain and maintenance of joint function. Pain relief is usually carried out with the use of simple analgesics (such as paracetamol) or nonsteroidal anti-inflammatory drugs (NSAIDs), or both; topical analgesics and rubefacients can also provide symptomatic relief. However, it has been suggested[6] that NSAIDs should only be tried when paracetamol is ineffective or when there is a significant inflammatory component. There has been concern that NSAIDs may accelerate osteoarthritis.[7] Misoprostol is sometimes administered with NSAIDs in an attempt to reduce gastro-intestinal adverse effects such as peptic ulceration and haemorrhage when the use of NSAIDs is considered essential. Systemic corticosteroids have no place in the management of osteoarthritis. Intra-articular or peri-articular injections of corticosteroids are somewhat controversial but may be of help in some patients with localised inflammation, though if used they should only be given infrequently. Improvement of symptoms has been obtained with intra-articular injections of sodium hyaluronate,[8] hylan,[9] or superoxide dismutases[10] but their place in the management of osteoarthritis is unclear. Other compounds being used or tried in osteoarthritis include adenetionine, diacerein, and glucosamine sulphate.

For further information on the agents mentioned above, see

Adenetionine, p.1(69)	Misoprostol, p.1469)
Corticosteroids, p.1017	NSAIDs, p.72
Diacerein, p.34	Paracetamol, p 81
Glucosamine, p.1711	Sodium Hyaluronate, p.1754
Hylan (see Sodium Hyaluronate, p.1754)	Superoxide Dismutase, p.99

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10. McIlwain H, *et al.* Intra-articular orgotein in osteoarthritis of the knee: a placebo-controlled efficacy, safety, and dosage comparison. *Am J Med* 1989; 87: 295–300.

Rheumatoid arthritis. Rheumatoid arthritis is a common chronic systemic inflammatory disease which predominantly affects the synovial joints. Early rheumatoid arthritis is characterised primarily by inflammation of the synovium, as the disease progresses the patient suffers destruction of cartilage and bone. Extra-articular features commonly include general malaise, fatigue, weight loss, fever, and anaemia. Features associated with more severe forms of the disease include vasculitis, pericarditis, pleurisy, pleural effusion, pulmonary interstitial fibrosis, peripheral neuropathies, subcutaneous and pulmonary nodules, scleritis, and Sjögren's syndrome.

The cause of rheumatoid arthritis is probably multifactorial. There may well be an immunological component because about 80% of patients with rheumatoid arthritis have raised serum concentrations of rheumatoid factors, which are antibodies directed against immunoglobulin G (IgG). However, these antibodies are also found in other diseases and their role is unclear in the pathogenesis of rheumatoid arthritis. Another hypothesis proposes that rheumatoid arthritis may be the result of some infectious agent.

The incidence of rheumatoid arthritis is initially higher in women than in men but equalises in later life and it has been suggested that androgens may have some sort of protective effect.

The severity and course of the disease varies greatly between patients. Disease activity usually fluctuates during the first few months and it is difficult to predict the course of the disease at this stage. Some patients will have a mild disease and may only experience brief attacks with little or no disease progression. However, the vast majority of patients will have intermittent relapses and remissions with an overall pattern of slowly progressive joint destruction and deformity. A few patients may have very severe and rapidly progressive disease.

Since there is no curative treatment yet for rheumatoid arthritis, management is aimed at alleviating pain and improving or maintaining joint function. This is accomplished through physiotherapy as well as the use of drugs. In some cases surgery may be required.

Many different drugs have been used. The choice of drugs for relief of pain depends upon the severity of symptoms. In mild cases an analgesic alone may be all that is required but most patients need the additional anti-inflammatory effect provided by a nonsteroidal anti-inflammatory drug (NSAID). Aspirin was once widely used, but has been superseded by other NSAIDs that are better tolerated. Although there is little apparent difference between the various NSAIDs in terms of anti-inflammatory activity and toxicity, patient responses vary widely. When starting an NSAID the dose should be gradually increased to the recommended maximum over one to two weeks and if the response is inadequate after a total of about four weeks, or if adverse effects are intolerable, other NSAIDs should be tried. Misoprostol is sometimes administered with

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NSAIDs in an attempt to reduce gastro-intestinal adverse effects such as peptic ulceration and haemorrhage.

Although NSAIDs provide symptomatic relief they do not suppress the rate of cartilage erosion or alter the course of the disease. Additional treatment has to be given to try to achieve that effect. The drugs that are used in this way are known as second-line agents. The use of second-line agents has conventionally been delayed until there is evidence of progressive disease, but many rheumatologists now add a second-line drug as early as they can to try to prevent irreversible joint damage. The rationale behind this decision appears to be confirmed by recent work which indicates that significant general skeletal bone loss occurs early in the disease.[1] Means to identify those patients most likely to benefit from early aggressive therapy are being studied.

Second-line agents are a diverse group of drugs with different structures and probably different modes of action and include the antimalarials (chloroquine, hydroxychloroquine), sulphasalazine, gold compounds (auranofin, sodium aurothiomalate), penicillamine, methotrexate, azathioprine, cyclophosphamide, chlorambucil, and cyclosporin. Current hypotheses on the modes of action of some second-line agents have been discussed.[2] Such second-line agents are often referred to as slow-acting antirheumatic drugs (SAARDs) as, unlike the NSAIDs, any therapeutic effect may not be apparent for 4 to 6 months. If, however, the response is inadequate after at least 6 months of therapy another second-line agent should be tried. The WHO have proposed a new classification of antirheumatic drugs[3] in which the term symptom-modifying antirheumatic drugs (SMARDs) is used to cover agents that improve signs and symptoms of inflammatory synovitis and the term disease-modifying antirheumatic drugs (DMARDs) is reserved for agents that have demonstrable sustained disease-modifying benefits. It was accepted that there might not be any agents that could presently be classified as DMARDs.

The long-term use of second-line agents is limited by toxicity and loss of efficacy. Drop-out rates in studies have been high and most patients do not continue to take a particular agent for more than one or two years. As adverse reactions frequently occur and may be life threatening, all patients require careful monitoring to avoid severe toxicity. Patients who relapse during treatment with one second-line agent may gain benefit when a different one is substituted. Treatment with more than one second-line agent has also been tried but there is little evidence of increased benefit overall. A meta-analysis[4] of 5 different combinations of second-line agents found that although efficacy might be greater than single agents, toxicity was also increased. However some combinations have produced favourable results.[5]

There is little agreement on which second-line agents should be used first and their selection is largely based on individual experience and preference. At present, data from comparative studies are insufficient to allow more than a crude ranking of the second-line agents with regard to efficacy and toxicity but a number of reviews and analyses have been published to aid the rational selection of these agents in rheumatoid arthritis.[6-16] Some meta-analyses[6,8] of generally short-term comparative studies suggest that methotrexate, intramuscular gold (sodium aurothiomalate), sulphasalazine, and penicillamine are more or less equivalent in efficacy, while the antimalarials and oral gold (auranofin) appear to be somewhat less effective. Intramuscular gold exhibited the highest toxicity while the antimalarial agents and oral gold had relatively low toxicity rates.[6] Another meta-analysis[7] considered that antimalarial drugs and methotrexate had the best ratio of toxicity to efficacy.

Intramuscular gold has long been used for the treatment of rheumatoid arthritis and is often the standard against which the efficacy of other treatments is measured. Although it is still extensively prescribed, its toxicity and poor long-term efficacy has led to renewed debate over its place in antirheumatic therapy.[17,18] Oral gold is less toxic but is also much less effective. Early enthusiasm for penicillamine has also been somewhat curtailed by poor long-term efficacy and a high incidence of adverse effects. The antimalarials are less effective than most other second-line agents but as they are generally less toxic and better tolerated they may be preferred in patients with milder forms of disease. Although sulphasalazine was originally introduced for the treatment of rheumatoid arthritis results of early studies were unfavourable and it subsequently found its main use in the treatment of inflammatory bowel disease. However, reinvestigation many years later demonstrated its efficacy and some rheumatologists now use it as one of the agents of first choice. Immunosuppressants have also been used in rheumatoid arthritis but there are concerns over long-term toxicity. Recent work has shown that methotrexate can improve disease activity when given once weekly in low doses that are too small to produce systemic immunosuppression. When methotrexate is used in this manner adverse effects occur commonly but are usually mild. In a recent long-term study[19] almost two-thirds of patients were still taking methotrexate after 5 years. The risk of hepatotoxicity remains a concern and guidelines for monitoring patients receiving methotrexate have been published.[20] None the less, some rheumatologists[14] consider methotrexate to be a first-line agent. Improvement generally begins earlier with methotrexate than with other second-line agents. Concomitant use of folic acid or folinic acid is recommended by some as this can reduce the toxicity of methotrexate without reducing efficacy,[21,22] but the timing of administration may be important. The use of other immunosuppressants is more debatable but azathioprine, cyclophosphamide, and chlorambucil are still used in some patients with severe disease who have failed to respond to other agents especially in those with extra-articular manifestations such as vasculitis. Cyclosporin has also been shown to be effective in rheumatoid arthritis but because of concern over nephrotoxicity it is considered that it is best reserved for refractory patients.

The use of corticosteroids in rheumatoid arthritis is controversial. Although systemic corticosteroids can suppress the symptoms of the disease their usefulness is limited by adverse effects and they are usually reserved for use in patients with severe rapidly progressing disease that has failed to respond to other antirheumatic agents or when there are severe extra-articular effects. However, some rheumatologists consider that they may also be useful for severe arthritis in elderly patients where the benefits outweigh the long-term risks. Systemic corticosteroids have also been used temporarily to control disease activity during initiation of second-line agents. Intra-articular injections of corticosteroids may be used when there are acute flares affecting one or two individual joints but should be given infrequently. In spite of problems with the adverse effects of corticosteroids it has been suggested that, in line with current thinking on the earlier use of more aggressive therapy for the control of inflammation, early use of short-term corticosteroids might also be appropriate,[23] and recent work indicates that patients with early active rheumatoid arthritis might benefit from low-dose corticosteroid therapy.[24] Although corticosteroids are associated with bone loss[25] this appears to be dose-related[26] and at some doses the benefits of corticosteroid therapy on inflammation and mobility might result in a reduced loss of bone in patients with rheumatoid arthritis. It has been suggested that for this type of treatment the dose should probably be restricted to 5 to 7.5 mg of prednisolone daily.[25]

A wide range of other agents has been tried in rheumatoid arthritis,[9,15,27,28] including green-lipped mussel, ketotifen, phenytoin, and various anti-infective agents such as inosine pranobex, metronidazole, and rifampicin, but there is little clearcut evidence of efficacy. Studies[29,30] indicate that minocycline can produce modest beneficial effects in patients with rheumatoid arthritis but the clinical significance of these improvements has been questioned[31] and it remains to be determined what role if any minocycline would have in the management of rheumatoid arthritis. The androgen stanozolol has produced some benefit but masculinising effects in female patients were considered unacceptable. Much research has been conducted into using immunomodulators and immunotherapy. Levamisole was found to be effective but is too toxic to use. Dapsone is little used, probably because of its weak activity and fears over toxicity.[32] Interferons have produced results similar to conventional second-line agents but the need for repeated injections is a drawback. Thymopentin has produced some encouraging results but its use may also be limited by the need for injection. Other agents being investigated include amiprilose, oral desensitisation with collagen, tenidap, immunoglobulins, and various monoclonal antibodies such as monoclonal antibody to tumour necrosis factor (interleukin inhibitors and cytokine modulators are still mainly at the experimental stage. Some studies suggest that addition of fish oils and/or evening primrose oil to standard antirheumatic therapy might help to reduce pain and joint swelling.

Findings that significant skeletal bone loss occurs early in the disease[1] have raised the question of the need for general measures to prevent osteoporosis in patients with rheumatoid arthritis.[33] Some[33] consider the use of oestrogen therapy in postmenopausal women with rheumatoid arthritis to be appropriate but to date the overall effect of such treatment is unclear.[33,34] The use of bisphosphonates such as disodium pamidronate is being studied.

The treatment of rheumatoid arthritis during pregnancy presents its own problems; the rational selection of suitable agents has been discussed in a number of reviews.[35-37]

For further information on the agents mentioned above, see

Amiprilose, p.1674
Androgens and Anabolic Steroids, p.1469
Aspirin, p.17
Auranofin, p.22
Azathioprine, p.544
Chlorambucil, p.550
Chloroquine, p.462
Collagen, p.1692
Corticosteroids, p.1017
Cyclophosphamide, p.554
Cyclosporin, p.557
Dapsone, p.220
Disodium Pamidronate, p.781
Evening Primrose Oil, p.1708
Fish Oils (Omega-3 Triglycerides, p.1510)
Folic Acid, p.1361
Folinic Acid, p.1362
Green-lipped Mussel, p.1712
Hydroxychloroquine, p.467
Immunoglobulins, p.1631
Inosine Pranobex, p.652
Interferons, p.653
Ketotifen, p.1443
Levamisole, p.116
Methotrexate, p.584
Metronidazole, p.621
Minocycline, p.250
Misoprostol, p.1460
Monoclonal Antibodies, p.1687
NSAIDs, p.72
Oestrogens, p.1471
Penicillamine, p.989
Phenytoin, p.380
Prednisolone, p.1054
Rifampicin, p.268
Sodium Aurothiomalate, p.94
Stanozolol, p.1506
Sulphasalazine, p.1243
Tenidap, p.99
Thymopentin, p.1760

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Spondyloarthropathies. The spondyloarthropathies are a group of seronegative arthritides which include ankylosing spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disorders (enteropathic arthritis), and arthritis associated with infection such as in reactive arthritis (aseptic arthritis) and Reiter's syndrome. The general management of these disorders has been reviewed.[1]

Ankylosing spondylitis is characterised by arthritis of the sacroiliac joints and sometimes there is also asymmetrical peripheral involvement. Males under 40 years of age are predominantly affected. The aim of management of the disease is to reduce pain and stiffness and to prevent joint deformity and this is accomplished using a combination of active physical therapy and drug therapy. Exercises are used to strengthen muscles and to maintain a good posture and range of movement in joints while nonsteroidal anti-inflammatory drugs (NSAIDs) are used to relieve pain and inflammation, thus allowing the exercises to be performed. Some patients may require concomitant treatment with analgesics such as paracetamol for pain control. Indomethacin has been considered by some to be the NSAID of choice although individual patient tolerance and preference often dictate the final choice of agent. Misoprostol is sometimes administered with NSAIDs in an attempt to reduce gastro-intestinal adverse effects such as peptic ulceration and haemorrhage. Phenylbutazone is sometimes used when other agents are unsuitable but it should be noted that the use of phenylbutazone in the UK has been limited to hospital rheumatology departments because of the risk of occasional serious adverse effects. Systemic corticosteroids are rarely indicated but intra-articular injections of corticosteroids may be beneficial when one or two peripheral joints are severely affected. Although NSAIDs reduce inflammation in ankylosing spondylitis they do not influence the progression of the disease. The second-line or slow-acting antirheumatic drugs (SAARDs) such as gold and penicillamine are also ineffective. A recent review[2] of ankylosing spondylitis concluded (that sulphasalazine appeared to be the only second-line agent that showed evidence of suppressing disease activity and suggested that it is worth using in patients with high disease activity, peripheral arthritis, or spondylitis of a short duration.

Psoriatic arthritis (or psoriatic arthropathy) is an inflammatory seronegative arthritis occurring in patients with psoriasis. In some patients the spine may be involved when the condition may be indistinguishable from ankylosing spondylitis. Less frequently some patients have a form of symmetrical arthritis resembling rheumatoid arthritis. The psoriasis and the arthritis usually require separate treatment. For a discussion of the management of psoriasis, see p.1079. Treatment of the arthritis is initially as for ankylosing spondylitis with NSAIDs and physical therapy. If these methods fail treatment with a second-line agent should be instituted. Gold compounds have been tried. Immunosuppressants such as azathioprine or methotrexate may be useful for severe or progressive cases but potential liver toxicity may limit the long-term use of methotrexate in some patients. Sulphasalazine has also been tried in some patients.[3] The use of antimalarials is controversial (see p.464) and should preferably be avoided. Systemic corticosteroids have no place in the management of psoriatic arthritis. Etretinate has produced some promising results and appears to improve both the arthritis and associated skin lesions.[4]

Reactive arthritis is treated with physical therapy and NSAIDs and if indicated intra-articular injections of corticosteroids; the role of antibiotics is less certain.[5] For a discussion of the use of antibiotics in the treatment of reactive arthritis see under Bone and Joint Infections, on p.135.

For further information on the agents mentioned above, see
Antimalarials (Chloroquine, p.462; Hydroxychloroquine, p.467)
Azathioprine, p.344
Corticosteroids, p.1017
Etretinate, p.1086
Gold Compounds (Auranofin, p.22; Sodium Aurothiomalate, p.93)
Indomethacin, p.51
Methotrexate, p.584
Misoprostol, p.1460
NSAIDs, p.72
Paracetamol, p.81
Penicillamine, p.989
Phenylbutazone, p.90
Sulphasalazine, p.1243

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Aceclofenac (2545-k)

Aceclofenac (*BAN, rINN*).
[o-(2,6-Dichloroanilino)phenyl]acetate glycolic acid ester; 2-(2,6-Dichloroanalino)phenylacetoxyacetic acid.
$C_{16}H_{13}Cl_2NO_4$ = 354.2.
CAS — 89796-99-6.

Aceclofenac, a phenylacetic acid derivative related to diclofenac, is a nonsteroidal anti-inflammatory drug (see p.72).

Studies[1,2] suggest that 100 mg is the optimal oral analgesic dose of aceclofenac. Aceclofenac has also been tried intramuscularly.[3]

The management of pain is discussed on p.3.

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Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Spain: Airtal; Falcol; Gerbin; Sanein.

Acemetacin (12309-x)

Acemetacin (*BAN, rINN*).
Bay-f-4975; TVX 1322. O-[(1-p-Chlorobenzoyl-5-methoxy-2-methylindol-3-yl)acetyl]glycolic acid.
$C_{21}H_{18}ClNO_6$ = 415.8.
CAS — 53164-05-9.

Acemetacin, a glycolic acid ester of indomethacin is a nonsteroidal anti-inflammatory drug (see p.72). Its pharmacological activity is due to both acemetacin and its major metabolite indomethacin (see p.51). Acemetacin is used in musculoskeletal and joint disorders and for postoperative pain and inflammation. For discussions of the management of these disorders and of postoperative pain, see p.10 and p.9. Usual daily doses are 120 to 180 mg by mouth in divided doses. Acemetacin is eliminated by both hepatic and renal routes and pharmacokinetics are not affected by moderate renal or hepatic impairment.

References.
1. Jones RW, *et al.* Comparative pharmacokinetics of acemetacin in young subjects and elderly patients. *Br J Clin Pharmacol* 1991; 31: 543–5

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Aust.: Rheumon; *Belg.:* Altren; *Ger.:* Rantudil; *Ital.:* Acemix; Solan; *Spain:* Espledol. Oldun; Tarbis†; *Switz.:* Tilur. *UK:* Emflex.

Acetanilide (2603-e)

Antifebrin. *N*-Phenylacetamide.
C_8H_9NO = 135.2.
CAS — 103-84-4.

Pharmacopoeias. In *Fr.*

Acetanilide, a para-aminophenol derivative related to paracetamol, has analgesic and antipyretic properties. It has generally been replaced by safer analgesics.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Multi-ingredient preparations. *Fr.:* Gripponyl; *Spain:* Alegrinal.

Actarit (13756-g)

Actarit (*rINN*).
(*p*-Acetamidophenyl)acetic acid.
$C_{10}H_{11}NO_3$ = 193.2.
CAS — 18699-02-0.

Actarit is reported to be an immunomodulator. It is used in the treatment of rheumatoid arthritis.

References.
1. Nobunaga M. Long term administration study of a new DMARD actarit on rheumatoid arthritis. *Rinsho Iyaku* 1994; 10: 947–52.

Alclofenac (2605-y)

Alclofenac (*BAN, USAN, rINN*).
W-7320. (4-Allyloxy-3-chlorophenyl)acetic acid.
$C_{11}H_{11}ClO_3$ = 226.7.
CAS — 22131-79-9.

Alclofenac, a phenylacetic acid derivative related to diclofenac, is a nonsteroidal anti-inflammatory drug (see p.72). It has been used in musculoskeletal and joint disorders. Following reports of toxicity, especially skin reactions, it has been withdrawn from the market in several countries.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Belg.: Mervan; *Switz.:* Mervan.

Alfentanil Hydrochloride (12339-b)

Alfentanil hydrochloride is an opioid analgesic related to fentanyl. It has a rapid onset and shorter duration of action than fentanyl after single doses and is mainly given intravenously in general anaesthesia. Significant respiratory depression occurs with higher doses.

Alfentanil Hydrochloride (*BANM, USAN, rINNM*).
R-39209. *N*-(1-[2-(4-Ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-(methoxymethyl)-4-piperidyl)propionanilide hydrochloride.
$C_{21}H_{32}N_6O_3$,HCl = 453.0.
CAS — 71195-58-9 (*alfentanil*); 69049-06-5 (*alfentanil hydrochloride, anhydrous*); 70879-28-6 (*alfentanil hydrochloride, monohydrate*).

Alfentanil hydrochloride 109 µg is approximately equivalent to 100 µg of alfentanil.